

REMARKS

Applicants thank the Office for the attention accorded the present Application in the November 16, 2006, Office Action. In that Action, Claims 1-10 and 17-18 were rejected under 35 USC §103(a) as being unpatentable over Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. in view of Rork et al.

The Office admits that the references Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. do not expressly teach the incorporation of beta-blockers such as timolol, metoprolol, atenolol, and propranolol, and HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single dosage unit.

The Office cites Rork et al. for the proposition that Rork et al. teaches a sustained release system that can include beta-blockers such as timolol, metoprolol, atenolol, and propranolol and statin cholesterol lowering agents such as simvastatin, pravastatin, and lovastatin. The Office then concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers such as timolol, metoprolol, atenolol, and propranolol with HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single once-a-day dosage unit.

The Office relies on Rork et al. and the knowledge of one of ordinary skill in the art to establish a prima facie case of obviousness, and then responds to Applicants' previous arguments and prior numerous submissions of secondary evidence of

nonobviousness by stating that the arguments are not found persuasive.

The Office further continues to rely on In re Kerkhoven to state that evidence is required to overcome the prima facie obviousness rejection. Applicants respectfully traverse.

Applicants remind the Office of the **primary purposes** of Applicants' invention is to increase compliance with taking medications, especially when multiple medications are required, as well as to simplify compliance. Applicants further state in Applicants' specification that patients with cardiovascular disease commonly take multiple medications and that the problems with achieving compliance include the inconvenience and confusion that arises especially for older patients with taking multiple medications. (See page 4, lines 16-21). Applicants' invention is provided to increase compliance among patients required to take a beta-blocker and a cholesterol-reducing agent. It is Applicants' proposed single dosage unit of a cholesterol lowering medication and a beta-blocker that is one of the solutions to enhancing compliance with taking a beta-blocker, especially after a first myocardial event, that was not obvious at the time of Applicants' invention.

Applicants hereby incorporate their previous arguments and evidence as to the inapplicability of In re Kerkhoven. To recap the Office's counter arguments on the applicability of In re Kerkhoven in view of Applicants' arguments on the differences in mechanisms of action, the Office listed several examples in the pharmaceutical art of two or more drugs having different mechanisms of action but concomitantly employed

together. As Applicants have previously shown, the Office's rationale has no basis in logic. It is contrary to the Office's own obviousness analyses since, as shown by Applicants' arguments and evidence, the very same examples are all protected by patent, which presumably are nonobvious.

In addition, the Office's reliance on Rork et al. is misplaced. Rork et al. disclose a controlled-release delivery device. As Applicants have previously pointed out, Rork et al. disclosure only supports the controlled-release of a single, active, beneficial agent. No where in Rork et al. is there a suggestion to combine more than one active, beneficial agent. Applicants have asked the Office to cite the sections in the Rork disclosure that supports the Office's interpretation that the Rork disclosure teaches combining more than one beneficial agent. The Office has failed to provide the citation(s) in Rork. The logical conclusion is that the Office cannot respond to such a request because the Rork disclosure does not contain any sections that support combining more than one beneficial agent in Rork's controlled-release deliver device. Thus, the Office has failed to make out a prima facie case of obviousness since the Office's contention of the teachings of Rork are unsupported.

Even though Applicants believe that the Office has failed to properly support its prima facie case of obviousness, Applicants have provided evidence of the recognition of the problem, the need to solve the problem and the difficulties encountered in solving the problem. The classical indicia of nonobviousness is recognition of the need and the difficulties encountered by those skilled in the field. In re Dow Chemical Co., 847 F.2d

469, 5 USPQ2d 1529 (Fed. Cir. 1988).

Applicants' disclosure emphasizes that medication compliance is a problem. It further states that simplification is a desired goal to the inconvenience of taking multiple dosage units over a long period of time and to the confusion that arises especially for older patients with multiple medication regimens.

Applicants' previously submitted evidence supports Applicants' argument that there is a long felt need to solve the medication compliance problem. Medication compliance is a complicated problem. The studies have illustrated that the person of ordinary skill in the art has long recognized the problem but that the problem of medication compliance persists, especially with chronic disease such as cardiovascular disease.

The Office provides no teaching or suggestion in the prior art to combine the medications claimed by Applicants in a single dosage unit. The Office simply says "it would have been obvious to one of ordinary skill in the art to provide Applicants' claimed invention." Applicants, on the other hand, have provided studies performed after Applicants' reduction to practice to further confirm Applicants' nonobvious insight that compliance can be improved by simplification of multiple medication treatment regimens. The studies are further evidence that those of ordinary skill in the art have pondered on possible solutions to the problem of medication compliance, but that not one of the solutions suggested Applicants' claimed invention.

The Office proceeds to cite two additional clinical studies that are related to

cardiovascular disease (See Waeber et al., and Mounier-Vehier et al.). The studies show that once-a-day dosing can improve patient compliance. However, these studies do not teach combining medications to improve patient compliance where the problem, as stated in Applicants' disclosure, is compliance to a multi-medication regimen, not to improve compliance with a treatment regimen for a single drug therapy.

It is Applicants contention that compliance can be improved by simplifying the therapy regimen as well as reducing the number of different, individually administered medications, which contribute to individual non-compliance to medication therapy. Applicants have early on recognized that the use of single dose medication therapy for beta-blockers and cholesterol lowering agents could improve medication compliance.

In addition, Applicants have provided evidence showing unexpected results that certain combinations of drugs on all cause mortality in patients with ischaemic heart disease provided increased benefits over those of each drug individually, which was heretofore unknown, while others did not. Applicants' claimed single dosage unit is not only a simplification of multiple medication treatment regimens, which was nonobvious at the time of Applicants' invention and since confirmed as one solution to the adherence/compliance problem, but also provides unexpected results. The unexpected results are the greater reduction in odds for all cause mortality not achieved by either medication alone. Applicants' claimed invention garners the unexpected reduction in odds with the simplification of medication treatment regimens together in a single dosage unit.

The so-called objective criteria must always be considered, Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966), and given whatever weight is warranted by the evidence presented. See Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1572 (Fed. Cir. 1996) (considering failure of others to find a solution to the problem); Transmatic, Inc. v. Gulton Indus., Inc., 53 F.3d 1270, 1275 (Fed. Cir. 1995) (considering failure of others to make the invention).

Conclusion

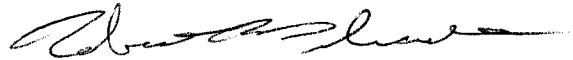
It is clear that, when Applicants' invention is viewed as a whole, the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit to enhance medication compliance. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. On the other hand, Applicants have provided evidence of the limitations in the prior art relied upon by the Office, the inapplicability of In re Kerkhoven, the noncompliance problems, the under-utilization of medications, and the unexpected reduction in odds for Applicants' combinations of cardiovascular medications for all cause mortality in patients with ischaemic heart disease, and confirmation that non-adherence or poor adherence to drug treatment is still a significant problem in the management of chronic diseases.

In light of the above arguments, Applicants respectfully submit that Claims 1-10 and 17-18 of the present application contain allowable subject matter and that the 35 USC §103(a) rejections have been successfully traversed.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,



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